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Hämetoja, Hanna

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Early stage minor salivary gland adenoid cystic carcinoma has favourable prognosis

Hanna Hämetoja^{1,2} · Karoliina Hirvonen³ · Jaana Hagström^{1,4} · Ilmo Leivo⁵ ·
Kauko Saarilahti⁶ · Satu Apajalahti⁷ · Caj Haglund^{4,8} · Antti Mäkitie^{3,9} · Leif Bäck³

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Abstract The purpose of the study was to evaluate the long-term outcome of minor salivary and mucous gland (MiSG) adenoid cystic carcinoma (ACC) of the head and neck and to compare the results with earlier reports including our recently published series on major salivary gland (MaSG) ACC. The study comprised 68 MiSG ACCs operated during 1974–2012 at the Helsinki University Hospital, Helsinki, Finland. Medical records and histological samples were reviewed. Our previously pub-

lished cohort comprising 54 MaSG ACCs during the years from 1974 to 2009 was used for comparison. The most common locations were the oral cavity and sinonasal cavities. Most patients presented stages IV (33.8%) and I (23.5%) disease. Primary treatment with curative intent, mainly surgery, was offered for 64 patients. Thirty-three (51.6%) of these patients developed a disease recurrence and 22 (66.7%) patients in less than 5 years. The difference in the length of recurrence-free time (<5 vs. >5 years) had an impact on OS and DSS ($p < 0.001$) showing worse prognosis for the earlier recurring group. T classes 2–4 ($p = 0.005$, $p < 0.001$, and $p = 0.001$, respectively) and stages II–IV ($p = 0.019$, $p < 0.001$, and $p = 0.002$, respectively) were associated with worse OS, DSS, and DFS. MiSG ACC had a similar long-term survival compared to MaSG ACC. Patients with stage I MiSG ACC seem to carry a favourable prognosis compared with those with stages II, III, and IV tumours. It is thus noteworthy that stage II tumours represent a truly advanced disease entity warranting a more aggressive treatment approach.

Karoliina Hirvonen shared first authorship

Antti Mäkitie and Leif Bäck have contributed equally

✉ Hanna Hämetoja
hanna.hametoja@helsinki.fi

¹ Department of Pathology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

² Department of Oral Pathology, University of Turku, Turku, Finland

³ Department of Otorhinolaryngology - Head and Neck Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

⁴ Research Programs Unit, Translational Cancer Biology Program, University of Helsinki, Helsinki, Finland

⁵ Department of Pathology, University of Turku and Turku University Hospital, Turku, Finland

⁶ Department of Oncology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

⁷ Department of Radiology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

⁸ Department of Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

⁹ Division of Ear, Nose and Throat Diseases, Department of Clinical Sciences, Intervention and Technology, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

Keywords Adenoid cystic carcinoma · Minor salivary gland · Malignancy · Oral cancer · Tumour · Prognosis

Introduction

Adenoid cystic carcinoma (ACC) is a salivary and mucous gland malignancy with poor long-term prognosis. It has a slow but persistent clinical course and diagnosis is often made at the advanced stage with occurrence of perineural invasion. ACC has a distinctive tendency to develop local and distant metastases at a late stage, even after one or two decades. According to our previous study on major salivary gland (MaSG) ACC, most distant metastases appear within a 10-year period [1].

The 2017 World Health Organization (WHO) classification of salivary gland tumours comprises 19 malignant entities.

ACC is denoted as the second most common malignancy [2]. Some nationwide studies from Finland, Denmark, and Pakistan, however, have reported that the most common salivary gland cancer in those countries is ACC [3–5].

The primary treatment for ACC is radical surgery with possible postoperative radiotherapy [6]. Chemotherapy is used in advanced, recurrent, or metastatic ACC. However, effective chemotherapeutic agents are lacking [6]. In the future, cumulative knowledge on genomic alterations of ACC may lead to novel chemotherapeutic treatments [7].

About 70% of all ACC cases originate in salivary glands. Minor salivary glands (MiSGs) are more often involved than MaSGs [8, 9]. ACC of MiSGs represents 2–4% of all head and neck malignancies [10, 11]. These typically appear in areas with salivary or mucous glands (i.e., in the oral cavity, oropharynx, sinonasal area, and upper respiratory tract) [12].

Most previous studies have included all cases of salivary gland ACCs, and only a few reports focus especially on MiSGs [9, 11, 13–17]. Therefore, the aim of this study was to investigate the clinical presentation, treatment, and outcome in the group of rarely investigated MiSG ACCs at a tertiary-care academic referral centre during a 38-year period and to compare the outcome to that of MaSG ACC. Moreover, our goal was to generate whole-population information based on regional data covering one-third of the Finnish population.

Materials and methods

We evaluated 68 patients with MiSG ACC who were treated between 1974 and 2012 at the Department of Otolaryngology, Head and Neck Surgery, Helsinki University Hospital, Helsinki, Finland. The previously reported 54 patients with MaSG ACCs were operated on during 1974–2009 at the same institution [1]. This single tertiary-care academic centre represents 1.6 million inhabitants, covering approximately one-third of the Finnish population.

We collected data on patient characteristics, histological parameters and clinical features of the tumour, treatment modalities, and survival outcome. Tumour size measurement was based on histological samples or identified from medical records. In three cases where there was inadequate tumour size information, the head and neck radiologist (S.A.) identified sizes from MRI images. An experienced head and neck pathologist (J.H.) confirmed the histopathological diagnoses using the histopathological diagnostic criteria validated and updated according to the WHO classification (2005) [18].

The Institutional Research Ethics Board approved the study concept (Dnro 31/13/03/02/2010, 01 February 2010). Statistics Finland provided the dates and causes of death. Overall survival (OS) was determined from the interval between the end of primary treatment and the last day of follow-up or the date of death. Disease-specific

survival (DSS) was defined as the interval between the last day of treatment and death due to disease. Disease-free survival (DFS) was determined as the interval between the last day of treatment and any sign of disease recurrence. All patients had a minimum follow-up of at least 3 years or until death.

Statistical analyses were performed using SPSS software (version 23.0, Chicago, IL, USA). We report values as medians with range for descriptive purposes. Calculations for survival rate were performed using the Kaplan-Meier method and survival functions by the log-rank test. Univariate associations of risk factors with OS, DSS, and DFS were analysed using Cox regression analysis. Risk factors associated ($p < 0.05$ in univariate analysis) with OS, DSS, or DFS were included in multivariable Cox regression model. The stage was not included in the same multivariable model with T class and neck metastases at presentation to avoid multicollinearity problems. Results are expressed using hazard ratios (HR) with 95% confidence intervals (CI). We considered p values <0.05 statistically significant.

Results

Patient characteristics

Table 1 shows patient and tumour characteristics of 68 patients with ACC. The current tumor, node, and metastasis (TNM) classification did not cover the six (8.8%) tracheal tumours. The TNM class could not be defined in four (5.9%) cases. Table 2 presents the relationship between tumour location and stage. Almost half of the tumours in the oral cavity ($n = 41$) were located in the palate ($n = 20$), with the hard palate being the most frequent site ($n = 15$).

Primary symptoms varied depending on tumour location. The most common clinical presentations were a lump (27.9%) and pain (17.6%). Symptom duration varied from 1 to 240 months with a median of 6 months. Three (4.4%) patients had a second malignancy at the time of diagnosis (prostate carcinoma, chromophobic renal cell carcinoma, or thyroid papillary microcarcinoma).

Preoperative investigations

The imaging methods used before treatment for most patients included computed tomography (CT) (57.8%) and magnetic resonance imaging (MRI) (45.6%) of the head and neck. Other examinations included chest CT scan (30.9%), ultrasound (16.2%), fine needle aspiration (11.8%), and positron emission tomography CT (5.9%).

Table 1 Characteristics of 68 MiSG ACC patients and the TNM classification for 62 tumours (trachea excluded)

	<i>n</i>	Percent
Sex		
Male	29	42.6
Female	39	57.4
Female/male ratio	1.35	
Median age, years (range)	58 (24–88)	
Tumour site		
Oral cavity	41	60.3
Paranasal cavities	6	8.8
Trachea	6	8.8
Nasopharynx	5	7.4
Oropharynx	3	4.4
Ear	4	5.9
Larynx	2	2.9
Oesophagus	1	1.5
T class		
T1	18	26.5
T2	12	17.6
T3	6	8.8
T4a	18	26.5
T4b	4	5.9
N/A	4	5.9
N class		
N0	54	79.4
N1	1	1.5
N2	1	1.5
N2B	1	1.5
N2C	1	1.5
N/A	4	5.9

N/A not available

Tumour characteristics

The median tumour size was 21 mm (range, 3–100 mm). For 19 (27.9%) tumours, size determination was not possible from clinical data, histopathological report, re-evaluation of the histological specimen, or MRI and CT images. The most common histopathologic growth pattern was cribriform (33.8%) followed by tubular (22.1%) and solid (8.8%) patterns. Most of the tumours showed a combination of growth patterns including tubular and cribriform (19.0%), solid and cribriform (7.4%), and solid and tubular (1.5%). Information on the growth pattern was not available in five (7.4%) cases. Tumours were classified under one growth pattern if more than 80% of the histologic sample was composed of that particular pattern. However, in cases with a combination of growth patterns, a pattern with more than 30% solid growth was classified into the solid group. Neural invasion (perineural, intraneural, or both) was present in 39 (57.4%) tumours. Information on neural invasion was not available for eight (11.8%) tumours.

Treatment

Most of the patients were treated with curative intent ($n = 64$, 94.1%). Approximately half of these patients ($n = 35$, 54.7%) received surgery only as their primary treatment. A neck dissection was performed in 17 (26.6%) cases; in 14 (82.4%) patients, the dissection was elective and in three (17.6%) patients, the dissection was therapeutic.

Twenty-four (37.5%) patients received postoperative radiotherapy to their primary tumour area. One (1.6%) patient received radiotherapy only with curative intent. The median radiation dose was 60 Gy (range, 32–70 Gy). Five (7.8%) patients received chemotherapy as part of the oncological treatment. One patient was lost to follow-up.

Four (5.9%) patients received palliative treatment only.

Table 2 ACC location and stage for 62 tumours

	Total 62	Stage I (<i>n</i> = 16)	Stage II (<i>n</i> = 12)	Stage III (<i>n</i> = 7)	Stage IV (<i>n</i> = 23)	N/A (<i>n</i> = 4)
Oral cavity (oc)	41	10	12	3	13	3
Palate	20	5	4	2	9	
Other oc	18	4	7	1	4	2
Upper lip	3	1	1			1
Oropharynx	3	3				
Nasopharynx	5			2	2	1
Paranasal sinuses	6				6	
Larynx	2	1			1	
Oesophagus	1			1		
Ear	4	2		1	1	

N/A not available

Outcome

Figure 1 shows a flowchart of the presentation of patients with metastatic disease across various sites at diagnosis and during follow-up. In 22 (66.7%) patients, the first appearance of their metastatic disease occurred within 5 years after treatment; nine (27.3%) patients later than 5 years after treatment. Patients with early metastatic disease had poorer OS and DSS than patients with no metastases during follow-up (Table 3) (Fig. 2). Among the patients treated with curative intent, the appearance of distant metastases was seen in 22 (66.7%) patients during follow-up. The most common location of distant metastasis was the lungs (64.0%), followed by bone (12.0%) and liver (12.0%). Information on the exact locations of metastases was not available in three (12.0%) patients. The mean interval for the detection of distant metastases was 43 months (range, 1–156 months). For the group

treated with curative intent, the 5-year Kaplan-Meier estimates for OS and DSS were 69.7 and 78.9%, respectively, and 10-year OS and DSS rates were 42.0 and 51.6%, respectively.

T classes 2–4 and disease stages II–IV were associated with poorer survival. No patients with T class 1 and stage I disease died of cancer (Fig. 3). In contrast, half of T classes 2–4 and stages II–IV patients died of cancer. Four patients had neck metastasis at presentation and this was associated with poorer OS and DSS, but not with DFS. Female gender and age < 65 were associated with better OS but not with DSS or DFS. Neural invasion was associated with poorer DFS (Table 3). However, neural invasion was not associated with the rate of local or locoregional recurrent disease. Appearance of distant metastases during follow-up was associated with poorer OS and DSS. Appearance of locoregional lymph node metastases was associated with poorer DSS but not poorer OS (Table 3). The solid growth pattern did not affect survival.

Fig. 1 Flowchart presenting the patient series. *NED* no evidence of disease, *AWD* alive with disease, *DOD* dead of disease, *DOC* dead of other cause, *N/A* not available, *mo* month

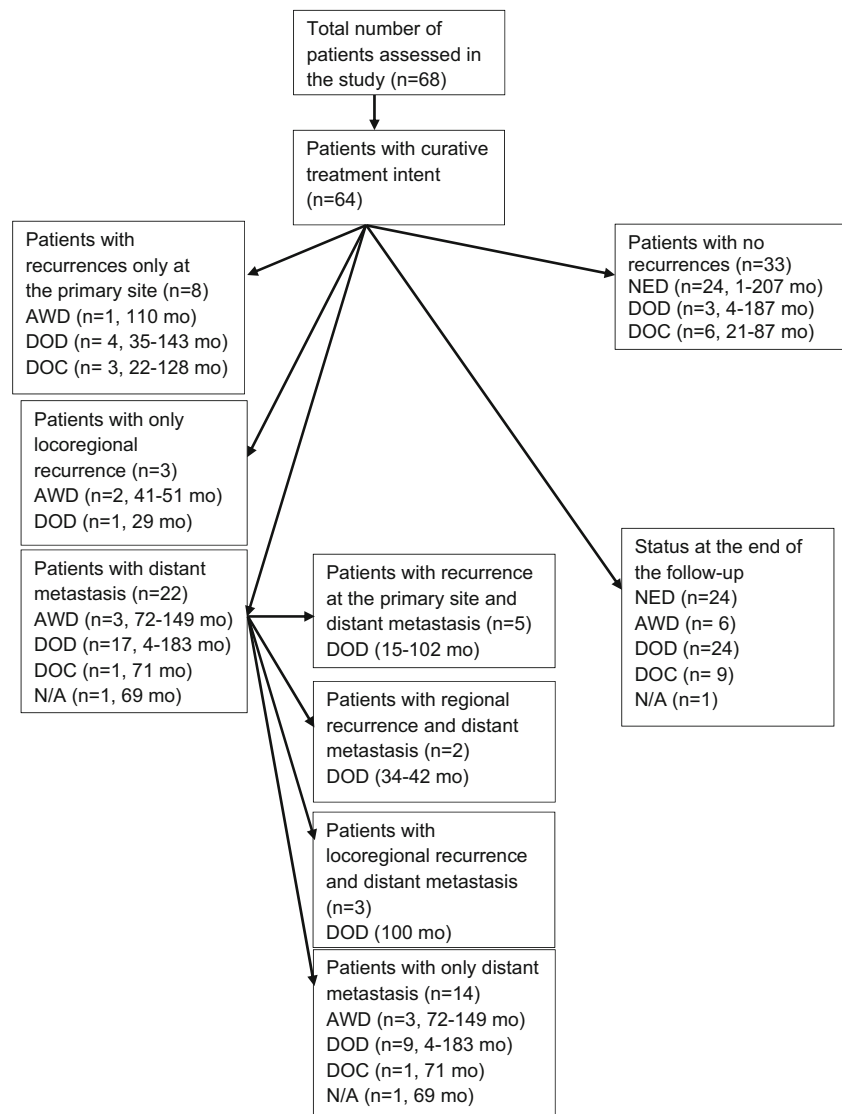


Table 3 OS, DSS, and DFS results of Cox regression analysis

	OS		DSS		DFS	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
T classes T2–4 vs. T1	4.72 (1.60–13.92)	0.005		<0.001*	8.59 (2.46–30.02)	0.001
Neck disease N+ vs. N0	7.37 (1.93–28.09)	0.003		<0.001	2.45 (0.56–10.79)	0.237
Stages II–IV vs. I	3.59 (1.23–10.47)	0.019		<0.001*	9.79 (2.27–42.26)	0.002
Male vs. female	2.32 (1.16–4.65)	0.018		0.087	1.93 (0.95–3.92)	0.070
Age >65 vs. <65 years	3.07 (1.39–6.75)	0.005		0.060	1.46 (0.67–3.19)	0.341
Neural invasion vs. no neural invasion	1.37 (0.60–3.13)	0.456		0.163	3.72 (1.28–10.80)	0.016
Early metastasis vs. no metastasis	4.65 (1.96–11.00)	<0.001	20.14 (4.39–92.42)	<0.001		
Late metastasis vs. no metastasis	1.91 (0.69–5.31)	0.216	5.07 (0.97–26.44)	0.054		
Primary metastasis	1.97 (0.98–3.93)	0.056	2.32 (1.03–5.21)	0.042		
Regional metastasis	2.50 (0.85–7.36)	0.096	3.81 (1.24–11.77)	0.020		
Distant metastasis	2.55 (1.26–5.16)	0.009	4.91 (1.93–12.46)	0.001		

OS overall survival, DSS disease-specific survival, DFS disease-free survival, HR hazard ratio, CI confidence interval

*Log-rank test. No patients with T class 1 and stage I disease died due to disease. Log-rank *p* values were thus used instead of HR with DSS

In multivariable Cox regression analysis, male gender, age > 65 years, T classes 2–4, stages II–IV, and neck metastases at presentation (N+) were associated with poorer OS. T classes 2–4 and stages II–IV were independently associated with poorer DFS, but neural invasion did not remain significant in multivariable analysis (Table 4).

Patients with stage I disease had a significantly better prognosis and survival than those with stages II, III, and IV disease. Even with disease failures, none of the stage I patients died of ACC. It is noteworthy that survival of stage II patients was significantly poorer than that of stage I patients, even though the treatment did not differ significantly.

Patients with stage I tumours

Sixteen patients had stage I disease. Three (18.8%) of these patients experienced disease failure; two local and one distant. Both patients with local failure had their primary tumour in the ear canal. The distant failure and one of the local failures appeared within 5 years. During follow-up, only one patient with local disease failure died; this was however due to causes other than ACC. Altogether, ten patients were alive with no evidence of disease and two with disease at the end of the follow-up (range, 36–204 months). Four patients died due to causes other than ACC.

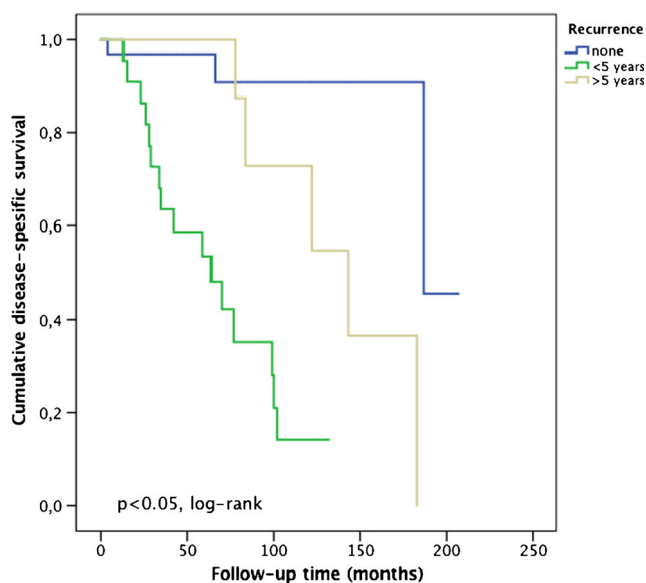


Fig. 2 Disease-specific survival of 64 patients treated with curative intent for minor salivary gland adenoid cystic carcinoma (no recurrence group, early-recurrence group (<5 years), and late-recurrence group (>5 years))

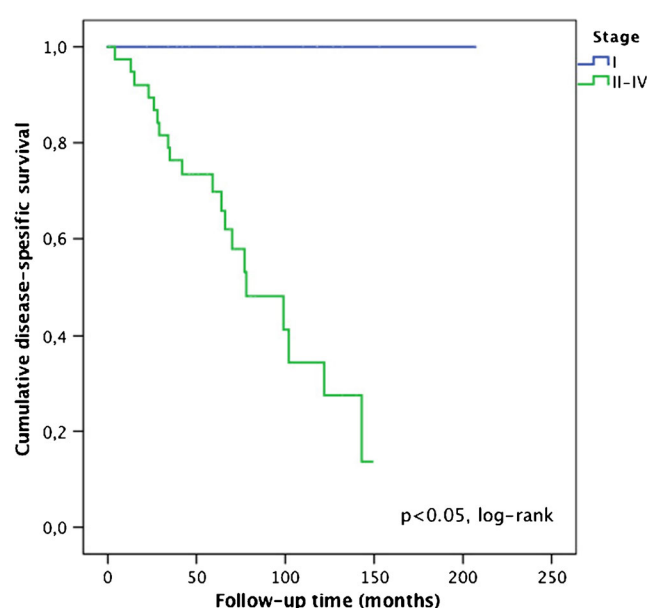


Fig. 3 Disease-specific survival of 64 patients treated with curative intent for minor salivary gland adenoid cystic carcinoma (stage I vs. stages II–IV)

Table 4 OS and DFS in multivariable Cox regression model

	OS model 1			OS model 2 ^b			DFS model 1			DFS model 2 ^b		
	Adjusted ^a HR (95% CI)	<i>p</i> value		Adjusted ^a HR (95% CI)	<i>p</i> value		Adjusted ^a HR (95% CI)	<i>p</i> value		Adjusted ^a HR (95% CI)	<i>p</i> value	
Male gender	2.67 (1.19–6.00)	0.017		3.05 (1.33–6.99)	0.008							
Age > 65 years	2.98 (1.31–6.77)	0.009		2.75 (1.21–6.24)	0.016							
Stages II–IV vs. I	4.07 (1.39–11.93)	0.011					7.48 (1.67–33.52)	0.009		8.27 (2.08–32.86)	0.003	
T classes 2–4 vs. I				5.58 (1.81–17.24)	0.003							
N+ vs. N0				3.94 (1.01–15.42)	0.049		2.58 (0.76–8.80)	0.130		3.45 (0.95–12.45)	0.059	
Neural invasion												

OS overall survival, DFS disease-free survival, HR hazard ratio, CI confidence interval

^a Adjusted for other factors in the model^b Stage was not included in the same multivariable model with T class and neck metastases at presentation to avoid multicollinearity problems

Patients with stage II tumours

Twelve patients had stage II disease; eight (66.7%) of these patients had disease failure. All cases in this group had their primary tumour located in the oral cavity. Five (62.5%) patients had disease failure within 5 years and three (37.5%) after 5 years. At the end of follow-up, four patients were alive with no evidence of disease, two patients were alive with disease, five had died due to disease, and one died due to other causes.

Patients with stages III and IV tumours

Seven patients had stage III disease; four (57.0%) of these patients experienced disease failure. Three (75.0%) patients developed metastatic disease within 5 years and one (25.0%) after 5 years. All patients with disease failure died due to the disease (range, 4–58 months) and the remainder were alive with no evidence of disease.

Twenty patients had stage IV disease; 14 (70.0%) of these patients experienced disease failure. Twelve (85.7%) disease failures appeared within 5 years and two (14.3%) after 5 years. Twelve patients died due to the disease (range, 13–143 months), and one patient was lost to follow-up.

Discussion

To characterize the behaviour and prognosis of MiSG ACC, we reviewed retrospective cases of 68 MiSG ACC patients treated between 1974 and 2012 in the Helsinki University Hospital region. According to our study, patients with stage I disease had good prognosis during follow-up and none died of ACC. On the contrary, advanced T class and advanced stage correlated negatively with OS, DSS, and DFS.

Our group recently reported a similar investigation on the ACC behavioural pattern in MaSGs [1]. Accordingly, we were able to compare these results between MiSGs and MaSGs. Only a few studies have reported separately the outcome of ACC in MiSGs and MaSGs [9, 11, 13–17, 19, 20] or compared ACCs in these different locations [21, 22].

In the present study on ACCs in MiSGs, the most common tumour location was the oral cavity (60%), with palate (49%) as the most frequent site as reported before [9, 13, 15, 16]. Among palatal tumours, the stage distribution was constant with slightly more advanced tumours (Table 2). In other intraoral sites, however, the tumours tended to be less advanced. On the contrary, in the series by Shum et al., palatal ACCs were predominantly of advanced T3–T4 classes (90%) [17]. Detection of palatal tumours may be clinically difficult compared to other intraoral sites, which might lead to diagnostic delay and allow extensive neoplasm infiltration consequently resulting in more advanced stages at presentation. It is

noteworthy in our series that ACCs of the nasopharynx and paranasal sinuses were all of advanced stage, although the number of these cases was limited. Furthermore, according to previous studies, ACCs of the paranasal sinuses are usually diagnosed late and the tumours are more advanced (T3–T4) [23–25]. It is possible that the nasopharynx and paranasal sinuses harbour tumour growth without early symptoms.

In previous studies, ACC has shown female predominance [9, 11, 13], which was also seen in our study (female to male ratio of 1.35). However, our previous study on MaSGs showed male predominance [1]. In the current study, female gender was associated with better OS, which may also reflect the higher life expectancy of women in general. On the other hand, a large series of head and neck ACC by Ellington et al. comprising 1754 MaSGs, 1117 oral cavity MiSGs, and 138 neck and pharynx ACCs showed a better prognosis for females [21].

Contrary to our study, earlier reports have not emphasized a good prognosis for stage I tumours in general, although similar findings for MiSG ACCs have also been reported. Mücke et al. did not find significant differences between stages I and II tumours, and other studies have also considered the behaviour of stage II tumours to be less aggressive [9, 15, 16]. DeAngelis et al. showed that T class was the only factor affecting survival, whereas Mücke et al. and Bianchi et al. both reported that T and N classes and stage affected survival [9, 15, 16]. In our study, T classes 2–4 and stages II–IV correlated negatively with OS, DSS, and DFS. The present results highlight the favourable survival of patients with stage I disease. For instance, none of the patients with a stage I tumour died due to the disease. The only treatment failures in this patient group occurred in patients with a tumour in the ear or in the oropharynx. Patients with an oral cavity ACC were free of disease failures. Disease-free surgical margins are probably easier to achieve for smaller tumours in the oral cavity than in the oropharynx or in the ear, which have a more complex anatomy. Both of the present stage I patients with ACC in the ear showed local disease failures, which highlights the complexity of surgical anatomy. On the other hand, two other patients with advanced stage ACC in the ear did not suffer from disease failures but were also treated more aggressively with surgery combined with radiotherapy. It might be feasible to consider more aggressive treatment also for stage I patients with ACC in this challenging location. According to our results, stage II disease in the oral cavity presents with poor outcome and with a high percentage of disease failures (67%). Considering these observations, patients with stage II ACC might benefit from more intensive treatment modalities. Similarly to MiSGs, advanced T class, N class, and advanced stage in MaSGs also had a negative effect on survival [1].

A well-known feature of ACC is neurotropism, which remains controversial considering that ACC metastasizes primarily haematogenously [26]. Neural invasion did not affect survival of MaSG ACC patients [1], but for the MiSG ACC

patients in the present study, neural invasion had a negative effect on DFS. In addition, neural invasion was not associated with the rate of either local, regional, or locoregional recurrences. Contrary to our findings, some studies have reported that perineural invasion affects treatment outcome of both MiSG and MaSG ACCs [14, 24, 27].

The growth pattern did not have an effect on survival. A solid pattern is related to poorer survival. According to the WHO, tumours with more than 30% of solid pattern have more aggressive behaviour [2, 18]. With MaSG, there was a slightly negative trend on survival but no statistically significant correlation was observed [1].

In both MiSG and MaSG, disease failures appearing within 5 years of the primary diagnosis significantly influenced OS and DSS. Primary and locoregional metastases negatively affected DSS in MiSGs but not in MaSGs. Distant metastases affected OS and DSS in both MiSGs and MaSGs. Most of the distant metastases appeared within 10 years in MiSGs and MaSGs [1]. Ellington et al. compared MiSG ACC to MaSG ACC and found decreased survival in MiSGs [21]. In the present study, long-term survival of MiSG ACC patients was similar to that of the MaSG ACC patients in our previous study [1].

The limitations of this study include its retrospective nature, which led to a shortage of necessary data on some single cases. Unfortunately, data concerning surgical margins were not sufficient enough to produce a reliable statistical assessment. The diagnostic assessment and treatment approach has also varied slightly during the course of the study. However, we were able to retrieve follow-up data covering a lengthy time period for all patients except one. Although our sample size was limited to only one tertiary-care academic centre, the number of the cases was large when compared to previous studies on MiSG ACC.

Conclusions

Patients with stage I ACC seem to have a good prognosis differing from that of patients with stage II tumours. Therefore, stage II tumours should be considered as truly advanced disease, which warrants a more aggressive treatment approach. As most disease failures tend to appear within approximately 10 years, we recommend an extended follow-up time of 10 years for MiSG ACC patients.

Compliance with ethical standards The Institutional Research Ethics Board approved the study concept (Dnro 31/13/03/02/2010, 01 February 2010).

Conflict of interest The authors declare that they have no conflict of interest.

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